Colonization of *Lactobacillus salivarius* in Patients Admitted to Intensive Care Units

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Learning objectives
- Explain the effects of an ICU stay on the gut microbiome
- List the benefits of probiotic use in healthy and hospitalized populations
- Define the role of *Lactobacillus salivarius* supplementation in the ICU population

Learning objectives

Agenda
- Overview of microbiome
- Microbiome effects on health
  - Probiotics
    - *L. salivarius*
  - Current research
  - Proposed methods
  - Summary
  - Questions

The human microbiome
- Consist of all microbe communities found within and on a human
- Considered its own organ
  - How many pounds of bacteria are on you?
- Accounts for approximately 150 fold more genes than our own human genome
- Established around two years of age
- Symbiotic relationship with host
- Affected by genetics, diet, environment, disease, stress...

The human microbiome

Impacts on health
- Antibiotic-associated diarrhea
- *C. diff* infections
- Late onset sepsis of preterm infants
- Neurologic disorders such as autism
- Development of atherosclerosis
- Irritable bowel syndrome
- Trauma shock-induced lung injury
- Multiple organ distress syndrome
- …and more

Impacts on health

Microbiome changes in the ICU
- Disease
- Metabolic stress
- Surgery
- Altered nutrition
- Medication
- Alter gut motility
- Alter availability of nutrients and oxygen
- Alter gut barrier

Microbiome changes in the ICU


Study of microbiome

- Important that we identify an accurate measure of microbiome composition
- Perfectly evolving snapshot that depicts the construction of our intestinal microbiome

Decreed diversity

- 80% ICU stool samples had decreased diversity
- ~50% ICU stool samples had extremely low diversity
- Healthy communities are replaced by low-diversity communities

Probiotics in the ICU

Probiotic benefits in the ICU

- Reduce risk of antibiotic-associated diarrhea and C. diff.-acquired diarrhea
- Improved intestine integrity
- Decreased ventilator-associated pneumonia
- Decrease ICU-acquired pneumonia
- Decrease ICU length of stay

Safety of probiotics

- 57 human clinical trials from the last 5 years (2008-2013)
- Quantity and nature of the reported adverse events (AEs)
  - AE= occurrence of a complication or illness, or worsening of the condition throughout the study
- Examined 54 different strains of bacteria
Safety of probiotics in the ICU

- Use of broad spectrum antibiotics
  - Examples of broad spectrum antibiotics may include: Fluoroquinolones, Zosyn, Clindamycin, Imipenem, Meropenem, Carbopenem
- Suspected antibiotic-associated diarrhea
- Prolonged mechanical ventilation lasting greater than 24 to 48 hours
- Enteral nutrition

Indications in the ICU

- Use of broad spectrum antibiotics
  - Examples of broad spectrum antibiotics may include: Fluoroquinolones, Zosyn, Clindamycin, Imipenem, Meropenem, Carbopenem
- Suspected antibiotic-associated diarrhea
- Prolonged mechanical ventilation lasting greater than 24 to 48 hours
- Enteral nutrition

Contraindications in the ICU

- Neutropenia (ANC < 500)
- Immunosuppression such as in post-transplant (liver, HSCT, kidney)
- Mechanical ventilation < 24 hours
- Poor gastrointestinal function or obstruction
- Milk protein allergy
- Recent studies...

Examples of protocol

- OHSU critical care patients
  - Nancy’s kefir 1/3 cup TID
- Portland VA critical care patients
  - Oral: Nancy’s yogurt 3oz 2-3x/day
  - EN: Nancy’s yogurt 3oz 2x/day mixed with 150ml water

Lactobacillus salivarius

- Gram positive bacteria, rod shaped
- Found naturally in the ileocecal region
- Benefits
  - modulate the gut microbiome
  - stimulate the immune system
  - produce beneficial short chain fatty acids
  - inhibit fecal enzymatic activity
  - act as an antimicrobial agent
  - improve gut integrity
- Strain UCC118

Tight junction proteins

- Improved gut integrity

Miyazaki et al Am J Physiol Gastrointest Liver Physiol 2012
**L. salivarius- administration**

- Randomized controlled trial of 80 healthy volunteers
- All fed strain UCC118 (10^9 CFU) for 21 days
- Administration
  - control, n=40
  - fresh milk, n=20
  - fermented milk, n=20
- Collected stool samples for up to 100 days following cessation of feeding
- Monitored number of total lactobacilli UCC118 present in feces

Collins J., Microbial Ecology in Health and Disease, 2002

**L. salivarius- administration**

- Both fresh milk and fermented milk established colonization
- Five subjects were still excreting the probiotic lactobacilli 21 days post-cessation of feeding, while one subject was still colonized up to 100 days after feeding

Collins J., Microbial Ecology in Health and Disease, 2002

**L. salivarius- administration**

- Dr. Martindale MD PhD, Jessica Gutgsell RD MS candidate
- Does yogurt and probiotic pill work as good or better than probiotic pill alone to colonize the gut in a healthy population?
- Study population: 40 healthy participants
- Intervention: supplementation for 21 days
  - 20 probiotic pill alone
  - 20 yogurt and probiotic pill
- Dietary component
  - dietary factors affect colonization of UCC118
- Sample collection
  - 5 total collections
- Results?

**Thesis significance**

- Can we get *L. salivarius* to colonize in the intestines of an ICU population?
- If so, which method of administration works best?

**Study aim 1**

- Compare the ability of *L. salivarius* UCC118 to colonize the intestines of post-orthopedic trauma patients using two forms of administration: kefir and UCC118 probiotic pill combined or UCC118 probiotic pill alone.
- Hypothesis: UCC118 colonization of the intestine will be more successful when administered with kefir.

**Study aim 2**

- Identify factors that negatively affect the colonization of *L. salivarius* UCC118 in post-orthopedic trauma ICU patients
- Hypothesis: patients receiving antibiotics, abdominal surgery, altered forms of nutrition and/or febrile patients will have hindered colonization
General study design

- Randomized prospective clinical trial at the OHSU trauma ICU
- Independent variables:
  - Control: Nancy’s kefir
  - Intervention 1: Nancy’s kefir and UCC118 probiotic pill
  - Intervention 2: UCC118 probiotic pill alone
- Dependent variables:
  - Presence of L. salivarius

Probiotic

- Probiotic Capsule
  - Active Ingredients: 1x10⁸ CFU of Lactobacillus salivarius, UCC118
  - Metagenics
- Probiotic Kefir
  - Bifidobacterium lactis
  - L. acidophilus
  - L. casei
  - L. rhamnosus

Probiotic administration

- Control: Nancy’s kefir
- Intervention 1: Nancy’s kefir with probiotic pill
- Intervention 2: Probiotic pill alone

Study population

- Post-trauma orthopedic ICU patients
- Size: TBD, approximately 10-20/group

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Ability to give informed consent</td>
<td>Prolonged lack of bowel motility</td>
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<tr>
<td>Ages 18-65</td>
<td>Pregnant/lactating female</td>
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<tr>
<td>Access to GI or PO intake</td>
<td>Known allergy or hypersensitivity to study products</td>
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<td>Minimum APACHE score of 10</td>
<td>Inability to comply with study</td>
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<td>Minimum stay of 24hrs in the ICU</td>
<td>Contraindications for probiotics</td>
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<td>Inability to pass stool</td>
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Patient timeline

- Patient admitted to ICU
- Patient is consented
- Patient has their first BM (HD day 1-2)
- Patient completes study enrollment
- Patient has their second BM (HD day 2-4)
- Protocol begins

Sample collection

- DNA genotek: OMNIgene•GUT (OMR-200)
- Collection Protocol
  - Small sample is collected (ICU nurse/myself)
  - Coded for confidentiality
- Stored in -20 degree freezer for later analysis
  - Research and Testing Laboratories
  - 16S ribosomal RNA sequencing
Statistical analysis

- p-value of less than 0.05 will be considered statistically significant
- Aim 1: chi-square test
- Aim 2: logistic regression model

Limitations

- Not blinded
- Limitations in collecting/storing samples
- Inability to control for patient treatments (surgery, medication use) post-admission
- Small sample size

Summary

- Microbiome is an ever-evolving component to human health
- Under healthy conditions, the host and microbiome have a symbiotic relationship
- Probiotic are generally safe and may offer many benefits in an ICU population
- L. salivarius may strengthen epithelial tight junctions
- This study will strive to determine best administration protocols L. salivarius in an ICU population

Thank You!

100 trillion friends you didn't know you had

References


